Oral Oncology 45 (2009) 747–751

Contents lists available at ScienceDirect

Oral Oncology

journal homepage: www.elsevier.com/locate/oraloncology

Review

Immunotherapy for head and neck cancer ☆

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ARTICLE INFO

Article history:
Received 12 January 2009
Received in revised form 17 February 2009
Accepted 18 February 2009
Available online 12 May 2009

Keywords:
Cancer vaccines
Tumor antigens
Immunotherapy
Dendritic cells
Cytokines

SUMMARY

Overall survival for patients with squamous cell carcinoma of the head and neck (SCCHN) has not improved appreciably over the past few decades. Novel therapeutic approaches, such as immunotherapy, are under clinical investigation since the standard treatments are toxic and have not successfully controlled this disease with sufficiently high success rates. Cancer immunotherapy describes various techniques to expand and activate the immune system to control tumor growth in vivo, and clinical evaluation has so far demonstrated low toxicity. Immunotherapy appears to have the most applicability in settings of minimal residual disease and to reduce distant metastases after other therapeutic interventions, and its potential clinical value is now receiving intensive evaluation. Emerging forms of SCCHN immunotherapy involve both the use of monoclonal antibodies (mAb) that target growth factor receptors where immune activation appears to contribute to tumor cell lysis, as well as various forms of active vaccination strategies which activate and direct the patient's cellular immunity against the tumor. This article reviews immunotherapeutic strategies currently in clinical trials or under development for patients with SCCHN.

Introduction

The long-term survival for patients with squamous cell carcinoma of the head and neck (SCCHN) is <50%.[1] Standard treatments have failed to impact long-term survival in this patient population and are increasingly toxic. Adjuvant therapy has long been considered as a potential treatment modality to eradicate local, regional and metastatic microscopic disease.[2,3] Cancer immunotherapy is also being evaluated for adjuvant treatment of SCCHN, involving techniques to utilize the patient's anti-tumor immune response to recognize and reduce metastasis, recurrence, and incipient second primary tumors.[4]

Immunotherapeutic approaches usually require identification of tumor antigens (TA) expressed by SCCHN cells. Numerous TA have been identified as potential targets for immunotherapy in SCCHN cells, but very few are tumor specific, and usually there is some level of expression in surrounding tissues. In general, TA are short peptide sequences generated from unique or shared proteins expressed by the cancer cells, recognized by either the humoral or cell mediated components of the immune system.[5]

Briefly, TA fall into a few broad categories. Some antigens, such as CASP-8[6], are uniquely expressed by SCC, whereas CEA[7] and MAGE[8] are associated with different stages or differentiation lineages. A third class of TA are over-expressed in tumor cells, such as p53[9] or EGFR.[10] Immune recognition is possible due to higher levels of wild-type sequence TA peptides expressed by malignant and premalignant cells compared to normal tissues. Still, some antigens are mutated forms of proteins found in normal cells, for example p53[11] and CDK4.[12] Finally, viral encoded oncoproteins, like the well studied human papillomavirus (HPV)-derived E6 and E7[13,14] proteins or Epstein barr virus (EBV)-derived antigens[15], are unique to SCCHN cells, providing strong rationale for immune targeting through cancer therapy or prevention.

TA should possess certain characteristics such as unique or differential expression on malignant cells. Broadly applicability TA would be expressed at a sufficient level in a majority of patients' tumors and are important for tumor survival or malignant behavior. This ensures that antigen loss, to avoid immune detection, produces a negative effect on tumor cell growth and survival. Finally, a targeted antigen must generate a potent immunologic response, or a means to augment this response must accompany the immunotherapy. The discovery of the identity, antigenic source, and molecular sequence of TA has led to the design of a number of targeted immunotherapeutics for SCCHN. This article provides a brief

☆ Funding source: R01 DE19727

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doi:10.1016/j.oraloncology.2009.02.009

review of emerging forms of immunotherapy for SCCHN, with a specific focus on recent advances in anti-tumor vaccines and their effectiveness in oral oncology.

Antibody therapy

Targeting tumor cells with high-affinity antibodies is successfully utilized in the treatment of SCCHN. mAb with high affinities for TA are relatively feasible to manufacture in large quantities and have been shown to be clinically efficacious[16,17] and less toxic in comparison to traditional chemotherapeutic agents.[18] These factors have led to the recent use of TA specific mAb immunotherapy targeting the epidermal growth factor receptor (EGFR)[10] and vascular endothelial growth factor (VEGF).[19]

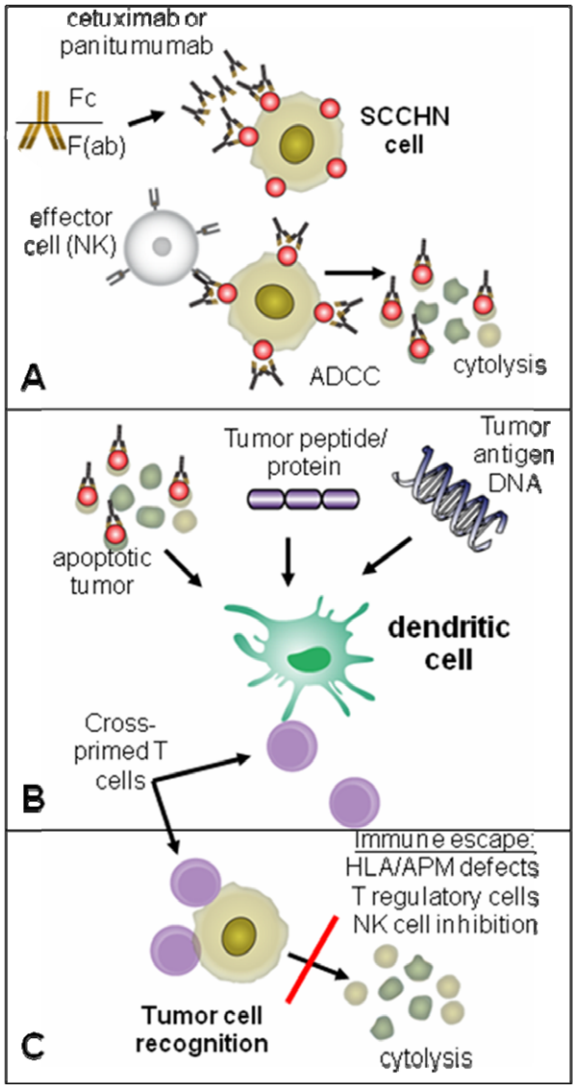

Figure 1 Schematic representation of ADCC, the effector mAb has a constant fragment [Fc] that interacts with immune effector cells, and a variable fragment [F(ab)] that is antigen (EGFR) specific. During cross presentation, tumor antigens are degraded in the cytoplasm of dendritic cells (DC), and presented to T cells producing a cellular immune response. Panel A: schematic representation of ADCC. The TA specific mAb has a constant fragment [Fc] that interacts with immune effector (NK) cells through a polymorphic FcγR, and a variable fragment [F(ab)] that is TA specific. This binding of mAb coated SCCHN cells to the FcγR-bearing NK cell leads to cytolysis. Panel B: during cross presentation, TA are transferred (taken up) into DC, degraded in the cytoplasm (termed TA processing), and presented to T cells producing a cellular anti-tumor immune response. Panel C: anti-tumor immune activity can be circumvented through multiple immune escape mechanisms, preventing SCCHN cell lysis and tumor outgrowth.

TA specific targeting of EGFR has been accomplished by two different FDA-approved mAb, cetuximab and panitumumab. More than 90% of SCCHN overexpress EGFR, and its importance in cell proliferation and survival, invasion and angiogenesis make it an attractive target for immunotherapy.[20,21] Cetuximab, a chimeric mAb targeting EGFR, was approved by the FDA in 2006 for use in combination with radiation therapy for treatment of locally advanced SCCHN. Phase II clinical trials have addressed the efficacy of combination cetuximab and radiation therapy,[22] as well as cetuximab and chemotherapy for locally advanced or recurrent SCCHN. In a Phase III trial of combination cetuximab, radiation therapy and cisplatin demonstrated 3 year overall survival, progression free survival and locoregional control rates of 76%, 56% and 71%, respectively.[23] Panitumumab has also been used in a Phase I trial with chemoradiation, showing clinical efficacy.[24] At the University of Pittsburgh, a Phase II trial of adjuvant panitumumab, cisplatin and radiation (UPCI 06-120) (Ferris, PI) is testing the ability of mAb panitumumab immunotherapy to reduce microscopic disease recurrence in high-risk, resected SCCHN patients.

Antibody mediated TA specific immunotherapy can may function through several mechanisms of action.[32,33] First, mAb may inhibit tumor growth by inhibiting signaling pathways involved in proliferation, differentiation and survival.[25] Second, mAb may serve as immunostimulants and induce innate (complement-mediated) immunity[26] or antibody-dependent cellular cytotoxicity (ADCC),[27,28] as well as inducing antigen-specific CTL via cross-priming.[29] Third, antibodies may serve as vehicles for the delivery of conjugated chemotherapeutic toxins to the tumor bed.[10] Fourth, mAb target SCCHN cell derived TA to DC for enhanced processing and cross-priming of T lymphocytes to broaden the anti-tumor immune response.[30,31]

Despite well documented clinical efficacy of EGFR specific mAbs[16] their mechanism of action is poorly understood. Clinical response to cetuximab therapy does not correlate with level of expression of EGFR, the targeted TA,[25] and likely involves more than simple competitive antagonism of receptor ligands. These mAb and cetuximab, the EGFR specific chimeric IgG1 mAb,[27] likely owe their clinical efficacy at least partly to antibody-dependent cell cytotoxicity (ADCC).[34,35] Natural killer (NK) cells participate in ADCC through binding of their NK FcγR (see Fig. 1 panel A) and polymorphisms at this FcγR have been implicated in clinical response.[34,36] Induction of TA specific T lymphocyte responses may also contribute to clinical responses. A number of investigators have demonstrated the importance of various arms of the immune system in clinical efficacy, and ultimately responses are likely multifactorial.

Vaccine strategies for SCCHN

Generation of an anti-tumor immune response involves many elements of the immune system, with T lymphocytes considered critical cellular effectors involved in anti-tumor activity. T cells recognize short peptide fragments (TA of 8–10 amino acids in length), derived from cellular protein antigens. These TA peptides are expressed by tumor cells and are also processed in antigen presenting cells from much larger proteins. These antigen presenting cells, such as dendritic cells (DC), display surface complexes composed of TA peptides bound to human leukocyte antigens (HLA) on the cell surface for recognition by T cells. It is these HLA:peptide complexes and adjacent costimulatory molecules which activate the T cells and ultimately produce anti-tumor activity (see Fig. 1 panel B). A major challenge of T cell based immunotherapies has been